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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/911,048	07/23/2001	Julian E. Davies	DAM 552-00	3719

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US ARMY SOLDIER AND BIOLOGICAL CHEMICAL COMMAND
OFFICE OF THE CHIEF COUNSEL/IP TEAM (BLDG E4435)
5183 BLACKHAWK ROAD
APG, MD 21010-5424

EXAMINER	
LU, FRANK WEI MIN	

ART UNIT	PAPER NUMBER
1634	6

DATE MAILED: 12/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/911,048	DAVIES ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restriction

1. Applicant's election of Group I, claims 1-15, species fluorescence spectrometry (claim 13) in Paper No. 5 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Sequence Rules Compliance

2. Figure 1 of this application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Direct the reply to the undersigned.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-13 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the qualitative and/or quantitative detection of

a ribosome inactivating protein by contacting a sample suspected of containing ribosome inactivating protein having a N-glycosidase activity with an oligonucleotide substrate having a GAGA tetraloop, does not reasonably provide enablement for a method for the qualitative and/or quantitative detection of ribosome inactivating protein by contacting a sample suspected of containing a ribosome inactivating protein without a N-glycosidase activity with an oligonucleotide substrate having a GA_XGA tetraloop wherein A_X is any kind of adenine derivative or analog. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court considered the issue of enablement in molecular biology. The Court summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims. The Court also stated that although the level of skill in molecular biology is high, results of experiments in molecular biology are unpredictable.

To begin, there is no direction or guidance in the specification to show that: (1) any kind of ribosome inactivating protein can release A_X from an oligonucleotide substrate having a GA_XGA tetraloop as recited in claims 1-13 and 15; and (2) A_X can be released from an oligonucleotide substrate having a GA_XGA tetraloop wherein A_X is any kind of adenine derivative

or analog as recited in claims 1-13 and 15. While the relative skill in the art is very high (the Ph.D. degree with laboratory experience), there is no predictability whether any kind of ribosome inactivating protein can release A_X from an oligonucleotide substrate having a GA_XGA tetraloop and whether any kind of A_X can be released from an oligonucleotide substrate having a GA_XGA tetraloop wherein A_X is any kind of adenine derivative or analog and can be detected by the method recited in claims 1-13 and 15.

The invention relates to a method for the qualitative and/or quantitative detection of a ribosome inactivating protein by contacting a sample suspected of containing any kind of ribosome inactivating protein with an oligonucleotide substrate having a GA_XGA tetraloop wherein A_X is adenine or any kind of adenine derivative or analog. An adenine derivative or analog as recited in claim 1 was read as a base such as G, C, T, U, and I and any of its derivative or analog. The specification (see pages 23-28) shows that a method for the qualitative and/or quantitative detection of a ribosome inactivating proteins having a N-glycosidase activity can be successfully performed using an oligonucleotide substrate having a GA_XGA tetraloop wherein A_X is A or 2-aminopurine although the specification does not specify that 2-aminopurine represents both 2-aminoadenine and 2-aminoguanine. Since it is well known in the art that ribosome inactivating proteins having a N-glycosidase activity cleave GAGA tetraloop of 28S ribosomal RNA and release adenine from **A** (the first A of GAGA tetraloop) (see Proc. Natl. Acad. Sci. USA, 99, 9581-9585, 1993; Kao et al., in Proceedings of the ERDEC Scientific Conference on Chemical and Biological Defense Research, pages 483-491, on November 17-20, 1998, at Aberdeen Proving Ground, MD, United States), it is unclear whether adenine from A_X in an

oligonucleotide substrate having a GA_XGA tetraloop wherein A_X is any kind of adenine derivative or analog can be released from the oligonucleotide when A_X in the GA_XGA tetraloop is substituted by other base such as G, C, T, U, and I and any of its derivative or analog since GAGA tetraloop has been changed. Furthermore, it is unclear whether any kind of ribosome inactivating protein can release adenine from A_X of an oligonucleotide substrate having a GA_XGA tetraloop since it is known that at least one kind of ribosome inactivating protein such as α-sarcin and restrictocin are endonucleases and do not have a N-glycosidase activity (see Table 1 in Kao et al.,).

Clearly, there will be a lot of unpredictable factors when the skilled artisan uses the claimed method in an oligonucleotide substrate having a GA_XGA tetraloop wherein A_X is any kind of adenine derivative or analog and the skilled artisan will have no way to predict the experimental results. Such efforts constitute undue experimentation. The undue experimentation at least includes to test: (1) any kind of ribosome inactivating protein can release adenine from A_X of an oligonucleotide substrate having a GA_XGA tetraloop; and (2) whether adenine from A_X in an oligonucleotide substrate having a GA_XGA tetraloop wherein A_X is any kind of adenine derivative or analog can be released from the oligonucleotide when A in the GAGA tetraloop is substituted by other base such as G, C, T, U, and I or any of its derivative or analog.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(f) he did not himself invent the subject matter sought to be patented.

6. Claims 1-5 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Kao *et al.,* (Proceedings of the ERDEC Scientific Conference on Chemical and Biological Defense Research, pages 483-491, on November 17-20, 1998, at Aberdeen Proving Ground, MD, United States).

Kao *et al.,* teach novel rapid method for the detection of ricin A-chain and related ribotoxins. Figure 1 showed two synthesized RNA substrates with a tetranucleotide GAGA loop for ricin (a ribosome-inactivating protein). As shown in Figures 2A, 2B, 2C, and 2D, the substrate were incubated with different amount of ricin at different times. The adenine released by ricin from the substrate was modified in the presence of bromoacetaldehyde and was detected using fluorescence spectrophotometer as recited in claims 3-5 and 13 (see pages 484-489). Since ricin cleavage site (N-glycosidase site) on 35 mer and 14 mer RNA was located in **A** of GAGA tetraloop (from 5' to 3', see Figure 1), the released adenine was considered to be from **A** (A_x in claim 1) of the G**A**GA tetraloop of 28S ribosomal RNA as recited in claims 1 and 2.

Therefore, Kao *et al.,* teach all limitations of claims 1-5 and 13.

7. Claims 1-5 and 13 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

The paper above was published from the laboratory of the inventors on November, 1998 and taught all limitations recited in claim 1-5 and 11. Note that there was an extra coauthor, T.

Orton in this paper which was not listed in this instant application. This coauthor was considered as a coinventor for this instant application because his or her name was listed in above paper.

8. Claims 1-5 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Zamboni *et al.,* (Biochem. J., 259, 639-643, 1989) as evidence by Szewczak *et al.,* (Proc. Natl. Acad. Sci. USA, 99, 9581-9585, 1993).

Zamboni *et al.,* teach high-pressure-liquid-chromatographic and fluorimetric methods for the determination of adenine released from ribosomes by ricin and gelonin, two ribosome-inactivating proteins (RIPs). In the fluorimetric assay, the experiment was performed by incubating rat liver ribosomes in the absence and presence of RIPs. At the end of incubations, one volume of cold ethanol was added and ethanol-soluble fractions were recovered by centrifugation. Free adenine present in the ethanol-soluble fraction was converted into its etheno derivative by reacting with chloroacetaldehyde as recited in claims 3-5. The adenine released was detected by measuring fluorescence of etheno derivative of adenine using spectrophotofluorimeter as recited in claim 13. Since it was known that large subunit of the ribosome comprised 28S ribosomal RNA (for detail, see any of Biochemistry Book) and ricin cleavage site on 28S ribosomal RNA was located in GAGA tetraloop as evidenced by Szewczak *et al.,* (see abstract in page 9581 and Figure 1 in page 9582), the adenine detected in the assay was considered to be released from **A** (the first A) of the GAGA tetraloop of 28S ribosomal RNA as recited in claims 1 and 2.

Therefore, Zamboni *et al.,* as evidence by Szewczak *et al.,* teach all limitations of claims 1-5 and 13.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claim 1, 6, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brigotti *et al.,* (Nucleic Acids Res., 26, 4306-4307, 1998) in view of Kao *et al.,* (1998) and Nuovo *et al.,* (US Patent No. 5,538,871, published on July 23, 1996).

Regarding claim 1, Brigotti *et al.,* teach a rapid and sensitive method to measure the enzymatic activity of ribosome-inactivating proteins (RIPs). In the array, 731-2981 of the pBR322 plasmid was amplified in the presence of [8-^{3}H]dATP by PCR and used as a substrate for measuring polynucleotide: adenosine glycosidase activity of three of RIPs. Free adenine released from [8-^{3}H] labeled 731-2981 of the pBR322 plasmid was measured by liquid scintillation counting. Note that one of RIPs used in the assay was ricin. As shown by Kao *et al.,* (see the

rejection under 35 USC 102), ricin cleavage site (N-glycosidase site) on 35 mer and 14 mer RNA was located in **A** of GAGA tetraloop (from 5' to 3', see Figure 1) and adenine was considered to be released from **A** (equalize to A_x in claim 1) of the GAGA tetraloop. Since [8-^{3}H] labeled 731-2981 of the pBR322 plasmid was cleaved with ricin and the [8-^{3}H] labeled adenine was released, the examiner reasonably concluded that 731-2981 of the pBR322 plasmid had a GAGA tetraloop and adenine was considered to be released from **A** (equalize to A_x in claim 1) of the GAGA tetraloop.

Brigotti *et al.,* do not disclose to generate a fluorescence labeled PCR product, release a fluorescence labeled adenine from the PCR product and detect the released adenine using fluorescence spectrophotometer as recited in claims 6 and 15.

Nuovo *et al.,* teach that both radioactive and fluorescence labeled dNTPs could be used in PCR (see column 11).

Kao *et al.,* teach to detect the labeled adenine using fluorescence spectrophotometer (see the rejection under 35 USC 102).

Therefore, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have generated a fluorescence labeled PCR product, released a fluorescence labeled adenine from the PCR product and detected the released adenine using fluorescence spectrophotometer as recited in claims 1, 6 and 15 in view of the prior art of Brigotti *et al.,* Kao *et al.,* and Eck *et al.*. One having ordinary skill in the art would have been motivated to modify the method of Brigotti *et al.,* because the simple replacement of one oligonucleotide substrate with one kind of label with known properties

(ie., [8-^{3}H]dATP) from another oligonucleotide with another kind of label with known properties (ie.,fluorescence labeled dATP) as a substrate of a ribosome inactivating protein would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

11. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kao *et al.,* (1998) as applied to claims 1-5 and 13 above, and further in view of Eck *et al.*, (US Patent No.6,034,233, priority date: May 4, 1990).

The teachings of Kao *et al.,* have been summarized previously, *supra.*

Kao *et al.,* do not disclose an oligonucleotide substrate comprising 2'-O-methylated nucleotides as recited in claim 8.

Eck *et al.*, teach synthesized oligonucleotide substrate comprising 2'-O-methylated nucleotides. This kind of oligonucleotide was more stable than a regular oligonucleotide since it was resistant to nuclease digestion (see columns 6, 15 and 16).

Therefore, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed an array as recited in claim 1 using a oligonucleotide comprising 2'-O-methylated nucleotides and

GA_XGA tetraloop as a substrate of ribosome inactivating proteins in view of the prior art of Kao *et al.,* and Eck *et al.*. One having ordinary skill in the art would have been motivated to modify the method of Kao *et al.,* because it was known in the art at the time the invention was made that an oligonucleotide substrate comprising 2'-O-methylated nucleotides was more stable than a regular oligonucleotide (see above) and more easily to handle, and the simple replacement of one regular nucleotide with known properties from a modified nucleotide with known properties (ie., 2'-o-methylated nucleotides) would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Conclusion

12. No claim is allowed.

13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official

Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the patent Analyst of the Art Unit, Ms. Chantae Dessau, whose telephone number is (703) 605-1237.

Frank Lu
November 22, 2002

Ethan Whisenant
Primary Examiner

Application No.: 09/911,048

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- [X] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [X] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [ ] 7. Other: _____

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

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